UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION **This document relates to**: *Track Three Cases*	**MDL No. 2804** **Case No. 17-md-2804** **Judge Dan Aaron Polster**

DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

EXHIBIT 32

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Full length article

Transitioning from pharmaceutical opioids: A discrete-time survival analysis of heroin initiation in suburban/exurban communities

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ABSTRACT

Introduction: Research identifying pathways to heroin use has typically been conducted among urban populations. This study examined heroin initiation following pharmaceutical opioid use in three suburban/exurban Southern California counties.

Methods: Interviewer-administered surveys collected data among 330 participants (65.9 % male; 63.9 % non-Hispanic white) whose initial use of any opioid was a pharmaceutical opioid. Retrospective discrete-time survival analysis identified predictors of heroin initiation, measured as self-reported age of first heroin use.

Results: Median age of first pharmaceutical opioid use was 17 years; 50.6 % initially acquired pharmaceutical opioids from an illicit source, 56.7 % first used pharmaceutical opioids for recreational purposes, and 86 % initiated heroin use. Average time from first pharmaceutical opioid use to first heroin use was 8.2 years. Drug/alcohol treatment (adjusted Hazard Ratio [aHR]: 0.67, 95 % CI: 0.50, 0.88) was associated with delayed time to heroin initiation. Obtaining opioids from non-medical sources (aHR: 2.21, 95 % CI: 1.55, 3.14) was associated with accelerated time to heroin initiation. Reporting supply problems with obtaining pharmaceutical opioids (e.g., unable to acquire pharmaceutical opioids) was associated with accelerated time to heroin initiation, but the magnitude of this effect was dependent on one's history of methamphetamine use ($p < 0.05$).

Conclusions: Time to heroin initiation following pharmaceutical opioid use was accelerated among those reporting supply problems and delayed among those with exposure to substance use treatment. Interventions interrupting supply of opioids might benefit from coordination with evidence-based medication-assisted treatment to minimize the risk of transitioning to heroin use, particularly among those with a long history of non-prescribed pharmaceutical opioid use.

1. Introduction

Non-prescribed pharmaceutical opioid (NPPO) use and opioid-related overdose continues to pose a major public health crisis, despite numerous efforts to prevent and mitigate the harms associated with opioids. In 2017, opioid-related overdose deaths, including both pharmaceutical opioids and illicit opioids such as heroin, accounted for the majority of all drug overdose deaths in the United States (Scholl et al., 2019). Additionally, the rise in NPPO use has coincided with a rise in heroin use and dependence (Cerda et al., 2015; Cicero et al., 2015, 2014; Jones, 2013; Palamar and Shearston, 2018).

Research examining the progression from pharmaceutical opioid use to heroin use has found costs, accessibility, and pharmacologic similarities to be major contributors to heroin initiation (Carlson et al., 2016; Compton et al., 2016; Grau et al., 2007; Mars et al., 2014). These patterns are well documented in national-level studies in which 80 % of heroin initiates previously reported pharmaceutical opioid abuse (Muhuri et al., 2013). However, evidence suggests that within the last 15 years, individuals reporting NPPO and/or heroin use are demographically different from individuals who used opioids in previous generations (Cicero et al., 2014). While urban heroin use remains a major contributor to opioid-related death, in the last 15 years, opioid-

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related overdose has become a leading cause of death in suburban, exurban (i.e., semi-rural), and rural communities (Cicero et al., 2014; Wheeler et al., 2015). Despite these geographic shifts, the majority of research on transitions from pharmaceutical opioid use to heroin use has occurred among urban populations (Cicero et al., 2018). Yet the process that drives the transition from pharmaceutical opioid use to heroin use is not well understood for geographically dispersed areas such as suburban and exurban communities. These areas are usually less well served by syringe distribution programs (Des Jarlais et al., 2015) and medication-assisted treatment services (Andrilla et al., 2019), and may lack a visible drug market where people who use drugs can easily be found by outreach workers seeking to refer them to available services (Hibdon and Groff, 2014; Saxe et al., 2001). This has implications for the types of interventions which might be effective to prevent transition to heroin use and stop NPPO use in non-urban environments.

Given that most studies identifying pathways from pharmaceutical opioid use to heroin use are centered in urban areas, this study sought to address a critical research gap by characterizing factors associated with heroin initiation among a sample of people residing in suburban and exurban communities whose initial use of any opioid was a pharmaceutical opioid.

2. Methods

2.1. Study setting

This study is based on data collected between November 2017 and August 2018, among 330 individuals with a history of prescribed and NPPO use who resided in three Southern California counties: Orange, San Diego, and Ventura (U01CE0022778, PI Davidson). Opioid-related overdose has become a leading cause of death in suburban and exurban communities (Cicero et al., 2014; Wheeler et al., 2015). Our study counties were chosen because all three have characteristics consistent with suburban/exurban areas, opioid-related overdose death rates at or above the statewide rate for California, and opioid prescription rates at or above the statewide average (State of California Department of Justice, 2016; California Department of Public Health, 2014). We defined suburban/exurban as commuter communities largely comprised of residential buildings with few social services for people who use drugs, rather than purely by population density. During the study period, San Diego County (population 3.3 million) had a single syringe distribution site, Ventura County (population 854,000) had three syringe distribution sites, and Orange County (population 3.2 million) had no syringe distribution service.

2.2. Data collection

Participants were recruited through a combination of: a) recruitment at community-based organizations providing direct services to people who use drugs (e.g., syringe distribution and overdose prevention programs); b) advertising with support groups for families of individuals experiencing substance use disorder; c) street recruitment; and d) 'snowball' or chain referral sampling in which participants referred other potentially eligible people to the study. Eligibility included being at least 14 years old, residing in the study region, and either: 1. Using pharmaceutical opioids other than how it was prescribed or obtaining them without a prescription (NPPO) in past 12 months or 2. Using heroin in the past 30 days where prior to first heroin use, participant used pharmaceutical opioids.

All data were self-reported. The survey was administered by trained interviewers who read each question and provided clarification when needed. Interviews took place at locations convenient to the participants where privacy could be maintained and covered sociodemographics, mental health status, medical history, lifetime substance use, overdose history, and involvement with substance use disorder (SUD) treatment. The survey took approximately 50 minutes to complete and participants were paid $40 in cash immediately after consent and prior to completing the survey. We used this procedure to reinforce the point that research participation is voluntary and the participant could end participation without penalty. As anticipated, no consented and paid participant left without completing the survey. Interviewers recorded participant responses using an internet-connected smartphone, with data collection software (Limesurvey 3.5) running on a server administered by the University of California, San Diego (UCSD). All study procedures were approved by the UCSD Research Ethics Board who determined this study presented no more than minimal risk to human subjects and provided a waiver of parental/guardian permission for participants ages 14 – 17.

2.3. Measures

The outcome variable was measured as age when heroin use was initiated subsequent to pharmaceutical opioid use. Age of first heroin use was retrospectively ascertained by asking participants if they ever used heroin and if yes, the month and year of first use. If a date (month/year) could not be recalled, participants were asked to provide the age of first use.

2.3.1. Demographic characteristics

Participants provided their gender, age, race/ethnicity, education, housing status in the past 3 months, and county of residence. Race/ethnicity was reported as White, Asian, Black, Hawaiian or other Pacific Islander, Latino, and Native American but due to limited sample size, was reclassified as Hispanic/non-Hispanic non-White (reference group) and non-Hispanic White. Housing status was reclassified as homeless (yes/no), defined as living on the street, park, canyon, shelter, hotel, or vehicle.

2.3.2. Illicit substance use and medical history

Participants self-reported lifetime use of benzodiazepines (obtained from a non-medical source), methamphetamine, and cocaine. The month/year of first use for each substance was ascertained. Participants also provided the month/year of past surgeries (including dental surgery), injuries requiring ambulatory care, and SUD treatment.

2.3.3. Pharmaceutical opioid use history

Participants were asked detailed questions about the temporality and sequential ordering of their pharmaceutical opioid and/or heroin consumption patterns over their life course. This included questions pertaining to the month/year of each use, type of opioid (heroin vs. pharmaceutical opioid), intent of use (therapeutic defined as using opioids for physical pain management, para-therapeutic defined as using opioids to help with stress/anxiety, and recreational defined as using opioids for fun or to get high), acquisition (medical vs. non-medical sources), modality (swallowed, snorted/smoked, injected), and reasons for changing anything about their opioid consumption pattern over their life course. Based on these responses, three binary time-varying variables (yes/no) were constructed to determine whether the following occurred in the time period before heroin initiation: 1) took pharmaceutical opioids para-therapeutically; 2) took NPPO to self-medicate for physical pain problems; and 3) obtained pharmaceutical opioids from non-medical source (e.g., friend, family, drug dealer). Two additional binary time-varying variables were created, based on survey responses, to assess the rationale for heroin initiation: 1) wanted to try a new method, something new, or I needed a break from the other method; and 2) had supply problems with obtaining pharmaceutical opioids (i.e., I couldn't get that pharmaceutical opioid anymore, the person/place I was getting it from no longer had any, the new type of opioid was the only thing I could get, and the person I was getting it from was arrested or left town).

2.4. Analysis

A discrete-time survival analysis identified the predictors of time to heroin initiation, measured as age of first heroin use, among individuals whose initial use of any opioid was a pharmaceutical opioid. A person-period data set was constructed by reorganizing the data such that each participant had multiple lines of data corresponding to each year of life that they were at risk for heroin initiation. The outcome variable was assigned a value of 0 before the occurrence of the event and a value of 1 during the year of life (i.e. age) in which first heroin use occurred. For participants providing the date of first heroin use, we derived the age of first use by subtracting their date of birth (month/year) from their date of first use (month/year). Among participants who reported only the year of first use (n = 157; 47.6 %), we assigned their month of first use as January. Participants who never initiated heroin use were censored at their age when interviewed.

The discrete-time model was estimated by maximum likelihood using a complementary log-log regression model (Allison, 1982). Time dependent predictors included first use of non-opioid illicit substances, pharmaceutical opioid use history, and medical history. Time dependent predictors were retained in the final regression model if the p-value < 0.10. Participants who were unable to recall the exact month/year (or age) of non-opioid illicit substance use (i.e., benzodiazepines, methamphetamine, cocaine) or a medical event (i.e., surgery, injury, substance disorder treatment) or who reported the occurrence of these events in the same year (or age) of heroin initiation were excluded from analysis since we could not determine the temporal order of events. The final model adjusted for gender, age, race/ethnicity, education, and county of residence. Further, because non-opioid illicit substance use may differ by prescribed and NPPO use patterns, we assessed potential interactions between non-opioid illicit substance use and pharmaceutical opioid use history in the discrete-time model. Kaplan-Meier analysis was used to examine the cumulative proportion of heroin initiation. Bivariate comparisons of heroin initiation were generated with Wilcoxon-rank sum or chi-square test statistics. Analyses were conducted in STATA 14.

3. Results

3.1. Sample characteristics

Table 1 displays the descriptive characteristics of the sample. The majority of participants were male, (65.9 %), non-Hispanic White (63.9 %) and homeless (50.8 %) with at least a high school education (79.7 %). The median age was 31 years (interquartile range [IQR]: 26–38; range: 19–76). The majority reported lifetime use of at least one non-opioid illicit substance (other than cannabis) with the most commonly reported substances being methamphetamine (92.1 %) and powder cocaine (92.7 %). Approximately one-third of participants reported methamphetamine (34.8 %) and powder cocaine (34.6 %) use prior to first pharmaceutical opioid use. Eighty-six percent (86.4 %) of the sample reported lifetime heroin use (by design, all participants used pharmaceutical opioids prior to heroin use). Compared to those who never used heroin (n = 45, 13.6 %), heroin initiates (n = 285, 86.4 %) were significantly more likely to be non-Hispanic White, homeless, and to have used crack cocaine during their lifetime. There were no significant differences in gender, education, and medical history between the two groups.

3.2. First pharmaceutical opioid use

Table 2 describes the acquisition, intent, and modality of first pharmaceutical opioid use. The median age of first pharmaceutical opioid use was 17 years (IQR: 14 – 20; range: 7–65) with half of participants (49.4 %; n = 163) acquiring their first pharmaceutical opioid from a medical provider. The remaining half (n = 167; 50.6 %) acquired their first pharmaceutical opioid from a non-medical source: 22.7 % (n = 75) had it given to them by a friend or family member, 17.9 % (n = 59) purchased it from a friend or drug dealer and 10.0 % (n = 33) stole it from someone or somewhere.

For the majority of the sample, their first use of any pharmaceutical opioid met our definition of NPPO use since they either used a pharmaceutical opioid other than how it was prescribed or used it without a prescription (n = 200; 60.6 %). The median age of first NPPO use was 18 years (IQR: 15 – 21; range: 7–69). Over one-third of the sample initially used pharmaceutical opioids for recreational purposes (n = 119; 36.1 %), 1.8 % (n = 6) used it para-therapeutically (i.e., for non-pain problems like stress or anxiety), and 18.2 % (n = 63) indicated multiple reasons for first use (e.g., combination of therapeutic, para-therapeutic, or recreational purpose). Further, 43.3 % (n = 142) of the sample initially took pharmaceutical opioids for therapeutic reasons (Table 2) of which a small subset (n = 12) obtained their first pharmaceutical opioid without a prescription and used it to self-medicate for pain-related problems, meeting our definition of NPPO use (data not shown). Participants used NPPO for a median of 11 years (IQR: 7 – 18; range: 0–49).

3.3. Transition from pharmaceutical opioids to heroin

Among heroin initiates (n = 285; Table 2), 62.1 % (n = 177) used NPPO prior to first heroin use and 28.4 % (n = 81) initially used their pharmaceutical opioids as prescribed, then transitioned to NPPO use before initiating heroin. Among the remaining heroin initiates, 9.5 % (n = 27) never used their pharmaceutical opioids in a non-prescribed manner before initiating heroin use.

The mean time from first pharmaceutical opioid use to first heroin use was 8.2 years (95 % CI: 7.3–9.2) among heroin initiates. However, the rapidity of transition differed by history of methamphetamine use and reporting supply problems with obtaining pharmaceutical opioids. Fig. 1 displays the mean number of years between first pharmaceutical opioid use and first heroin use across four subgroups. The shortest initiation period was among individuals experiencing supply problems who did not use methamphetamine prior to heroin initiation (5.1 years; 95 % CI: 3.5–6.7). This was followed by individuals with a history of methamphetamine use (among those without supply problems: 7.8 years; 95 % CI: 5.9–9.7; and among those with supply problems: 9.1 years; 95 % CI: 7.6–10.6). The longest transition period was among individuals not experiencing supply problems and not reporting methamphetamine use prior to heroin initiation (9.4 years: 95 % CI: 7.2–11.7).

3.4. Heroin use initiation

Results from the discrete-time survival analysis are presented in Table 3. Older age (AHR: 0.93, 95 % CI: 0.91 – 0.95) and receiving SUD treatment or counseling prior to heroin use (AHR: 0.67, 95 % CI: 0.50 – 0.88) were independently associated with a decreased hazard of (i.e., delayed time to) heroin initiation. In contrast, endorsing the reasons of wanting to try a new method, try something new, or needing a break from the other method (AHR: 1.56, 95 % CI: 1.15–2.10) and obtaining NPPO prior to heroin use (AHR: 2.21, 95 % CI: 1.55–3.14) were independently associated with an increased hazard of (i.e., accelerated time to) heroin initiation. The discrete-time model also included a significant interaction between methamphetamine use and supply problems with obtaining pharmaceutical opioids. The final adjusted model only included methamphetamine use, as this was the most common non-opioid illicit substance used prior to first pharmaceutical opioid use (34.8 %), followed closely by powder cocaine (34.6 %), and was the only non-opioid illicit substance with a p-value < 0.10.

To visualize the interaction effect, a Kaplan-Meier failure curve displaying the cumulative proportion of first heroin use was generated (Fig. 2). The highest cumulative proportion of first heroin use was

Table 1
Descriptive characteristics of sample of people using prescribed/non-prescribed pharmaceutical opioids [a], n = 330.

Characteristics	Total Sample n = 330	Initiated Heroin Use n = 285	Never used heroin n = 45	p-value
Demographics				
Male	216 (65.9 %)	181 (64 %)	35 (77.8 %)	0.069
Non-Hispanic White	211 (63.9 %)	190 (66.7 %)	21 (46.7 %)	0.009
Homeless	167 (50.8 %)	153 (53.9 %)	14 (31.1 %)	0.005
Education				
less than HS	67 (20.3 %)	55 (19.3 %)	12 (26.7 %)	0.387
HS	103 (31.2 %)	92 (32.3 %)	11 (24.4 %)	
some college	130 (39.4 %)	114 (40 %)	16 (35.6 %)	
college graduate	30 (9.1%)	24 (8.4 %)	6 (13.3 %)	
County				
Orange	152 (46.1 %)	138 (48.4 %)	14 (31.1 %)	< 0.001
San Diego	109 (66.0 %)	78 (27.4 %)	31 (68.9 %)	
Ventura	69 (20.9 %)	69 (24.2 %)	-	
Age (median, IQR)	31 (26-38)	31 (26-38)	31 (25-45)	0.049
Lifetime Illicit Substance Use (other than heroin and cannabis)				
Benzodiazepines[b]	243 (73.6 %)	209 (73.3 %)	34 (75.6 %)	0.753
Methamphetamine/speed	304 (92.1 %)	264 (92.6 %)	40 (88.9 %)	0.386
Crack Cocaine	183 (55.5 %)	168 (59 %)	15 (33.3 %)	0.001
Powder cocaine	306 (92.7 %)	267 (93.7 %)	39 (86.7 %)	0.092
Illicit Substance Use prior to 1st pharmaceutical opioid use				
Benzodiazepines[b]	59 (21.2 %)	48 (20 %)	11 (28.2 %)	0.244
Methamphetamine/speed	102 (34.8 %)	87 (34.8 %)	15 (34.9 %)	0.992
Crack Cocaine[c]	35 (11.1 %)	-	-	-
Powder cocaine	100 (34.6 %)	88 (35.6 %)	12 (28.6 %)	0.374
Medical History				
Ever injured and ambulance called	186 (56.4 %)	161 (56.5 %)	25 (55.6 %)	0.906
Ever had surgery	253 (76.7 %)	219 (76.8 %)	34 (75.6 %)	0.85
Received treatment for drugs/alcohol	277 (83.9 %)	239 (83.9 %)	38 (84.4 %)	0.921

[a] Pharmaceutical opioids included Buprenorphine, Codeine, Demerol, Dilaudid, Duragesic, Fentanyl, Hydrocodone, Hydromorphone, Kadian, Lorcet, Meperidine, Methadone, Morphine, MS Contin, Norco, Oxycodone, OxyContin, Percocet, Roxicodone, Suboxone, Subutex, and Vicodin.
[b] Benzodiazepines included as Klonopin, valium, Rohypnol, Xanax, Librium.
[c] To protect confidentiality, crack cocaine results stratified by heroin initiation were suppressed due to small sample size (n < 5) within one of the strata.

among participants reporting supply problems but no prior history of methamphetamine use; whereas the lowest cumulative proportion of first heroin use was among those with no history of methamphetamine use and no supply problems.

4. Discussion

The opioid overdose epidemic is one of the greatest public health crises of modern times and as a result, there is a need for multifaceted strategies to address the harmful consequences of NPPO and heroin use. However, approaches to mitigating the harms associated with pharmaceutical opioid use have had modest and inconsistent effects, and many have focused on monitoring and lessening prescribing behaviors (Brady et al., 2014; Yarbrough, 2018). Recent studies have noted that intervention efforts to decrease access to pharmaceutical opioids have coincided with increases in heroin use and heroin overdose (Castillo-Carniglia et al., 2019; Chen et al., 2019; Faryar et al., 2017; Kolodny et al., 2015; Pitt et al., 2018). This may be linked to pharmaceutical opioids becoming harder to obtain (Li et al., 2018). To some extent, our results complement these other studies in that we found a significant association between the inability to obtain pharmaceutical opioids, particularly non-prescribed opioids, and time to heroin initiation.

Illicit acquisition of pharmaceutical opioids was common. Almost half of study participants obtained their first pharmaceutical opioid from a family member/friend, purchased it from a drug dealer, or stole it. Among heroin users, the majority (90.5 %) reported NPPO use in the period immediately before their first heroin use. At the time of interview, three-fourths of the sample used NPPO for at least 7 years.

The average time to heroin initiation was about twice as long in this sample compared to what has been reported by Guarino et al. (2018) and Kelley-Quon et al. (2019) but was within range of the results reported by Carlson et al. (2016). Differences between studies are likely attributed to different study populations (i.e., adolescents and young adults), study designs (prospective vs. retrospective), and in the case of the other studies, a sole focus on the transition from NPPO to heroin. In our cross-sectional and retrospective design, the median age was 31 years and a minority of participants (< 10 %) initiated heroin following prescribed pharmaceutical opioid use. However, it should be noted that for the majority of heroin initiates in this study, NPPO use was reported in the period preceding heroin use, which is a trajectory consistent with the other studies (Carlson et al., 2016; Guarino et al., 2018; Kelley-Quon et al., 2019).

Overall, our results suggest that changes to one's supply of pharmaceutical opioids impacted progression to heroin initiation in a sample where most were obtaining pharmaceutical opioids through illicit routes (90.5 %) rather than through prescription (9.5 %). Furthermore, we observed a synergistic effect between reporting supply problems and methamphetamine use, such that the association between supply problems (e.g., I couldn't get that pharmaceutical opioid anymore) and time to heroin initiation was dependent on an individual's history of methamphetamine use. The fastest progression to heroin initiation was among those experiencing supply problems who had not used methamphetamine prior to heroin initiation. The slowest progression was among those without supply problems or a history of methamphetamine use. Those with a history of methamphetamine use took on average 2–4 more years to initiate heroin use compared to those reporting supply problems and no history of methamphetamine use.

Table 2
Opioid use among sample of people who used pharmaceutical opioids, n = 330.

	Overall n (%)
Acquisition of 1st pharmaceutical opioid	
By prescription	163 (49.4 %)
Given by a non-medical person (friend/family)	75 (22.7 %)
Purchased from someone other than a pharmacy (friend/drug dealer)	59 (17.9 %)
Stolen from someone or somewhere	33 (10.0 %)
Reason for 1st pharmaceutical opioid use	
Therapeutic (i.e., pain management)	142 (43.3 %)
Para-therapeutic (i.e., help with non-pain problems like stress or anxiety)	6 (1.8 %)
Recreational (i.e., to get high/for fun)	119 (36.1 %)
Some combination of therapeutic/para-therapeutic/recreational	63 (18.2 %)
Route of administering 1st pharmaceutical opioid	
Swallowed	284 (86.1 %)
Snorted/smoked	31 (9.4 %)
Injected	15 (4.6 %)
Transition Patterns	
Never used heroin	45 (13.6 %)
Ever used heroin	285 (86.4 %)
Prescribed pharmaceutical opioid use prior to heroin initiation	27 (9.5%)
Prescribed pharmaceutical opioid use followed by NPPO[a] use prior to heroin initiation	81 (28.4 %)
NPPO[a] use prior to heroin initiation	177 (62.1 %)
Age of 1st pharmaceutical opioid use (median, IQR)[b]	17 (14-20)
Age of 1st NPPO[a] use (median, IQR)[c]	18 (15-21)
Age of 1st heroin use (median, IQR)[d]	22 (19-28)
Duration of NPPO[a] use in years (median, IQR)[c]	11 (7-18)

[a] NPPO = non-prescribed pharmaceutical opioid use.
[b] Includes all participants (n = 330) regardless of whether their first pharmaceutical opioid was prescribed or non-prescribed.
[c] Number of participants reporting history of NPPO use, n = 303.
[d] Number of heroin initiates, n = 285.

Table 3
Predictors of heroin initiation among those with history of pharmaceutical opioid use, n = 299[a].

Predictor	Adjusted HR	95% CI		p-value
		lower	upper	
Age	0.93	0.91	0.95	< 0.001
Male	0.89	0.68	1.18	0.431
Non-Hispanic White	1.12	0.84	1.48	0.438
Homeless	1.37	1.05	1.78	0.021
Education (ref. < HS)				
HS	1.10	0.75	1.62	0.628
Some college	0.92	0.64	1.33	0.664
College grad	0.69	0.39	1.21	0.194
County of residence (ref. Orange)				
San Diego	0.75	0.55	1.03	0.075
Ventura	1.14	0.80	1.60	0.471
Age of 1st pharmaceutical opioid use	0.97	0.94	0.99	0.002
Received treatment/counseling for drug/alcohol prior to heroin initiation	0.67	0.50	0.88	0.005
Time-varying Predictors				
Reason for initiating heroin use: wanted to try a new method, try something new, or needed a break from the other method	1.56	1.15	2.10	0.004
Obtained pharmaceutical opioid from non-medical source	2.21	1.55	3.14	< 0.001
Interaction between methamphetamine (meth) use before heroin initiation and supply problems[b] before heroin initiation				
No meth use/No supply problems	ref.			
No meth use/Supply problems	3.11	1.79	5.41	< 0.001
Meth use/No supply problems	2.39	1.48	3.88	< 0.001
Meth use/Supply problems	1.87	1.14	3.06	0.013

[a] Of the n = 330 eligible participants, n = 31 (9%) were excluded from the discrete-time survival analysis because the onset of methamphetamine use and/or receipt of drug/alcohol treatment occurred in the same year (or age) of heroin initiation.
[b] Supply problems defined as inability to obtain pharmaceutical opioids with responses including I couldn't get that pharmaceutical opioid anymore, the person/place I was getting it from no longer had any, the new type of opioid was the only thing I could get, and the person I was getting it from was arrested or left town.

Given the retrospective nature of our data, we could not determine the circumstances in which methamphetamine use occurred, such as whether methamphetamine served as a substitute for pharmaceutical opioids, and how this may have delayed heroin initiation. As described by others, changes to drug markets, such as supply reduction and price increases, may result in changes to a person's drug preference (Horyniak et al., 2015). We did not ascertain participants' drug of choice, nor were we able to ascertain whether participants were co-using pharmaceutical opioids and methamphetamine. Yet, we know from other studies that methamphetamine use is significantly associated with heroin initiation (Banerjee et al., 2016; Goldman-Hasbun et al., 2019; Strickland et al., 2019). Our findings highlight the need for additional research on the patterns of opioid use within context of other illicit drugs, particularly stimulants. At a time when public health resources are focused on ending the opioid epidemic (Gostin et al., 2017), there is a risk that the physical and social harms of other drugs such as methamphetamine may be overshadowed (The Lancet, 2018; Ellis et al., 2018; Mital et al., 2018). Further, given that qualitative studies have found different motivations for initiated and sustained use of

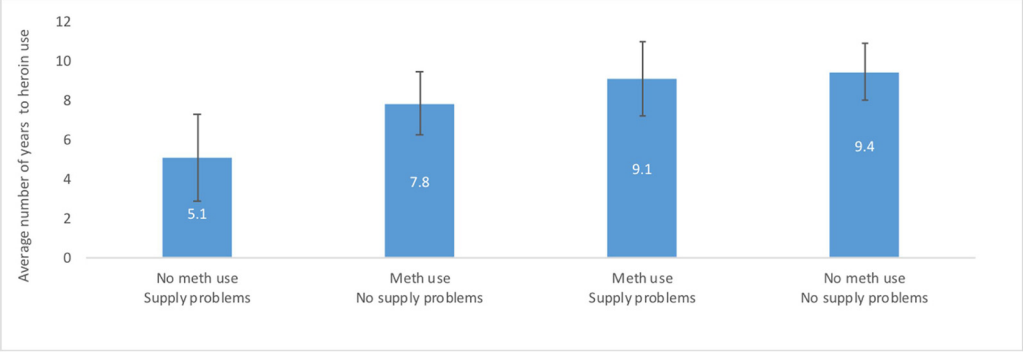

Fig. 1. Average number of years between first pharmaceutical opioid use and first heroin use across four groups classified according to history of methamphetamine (meth) use and supply problems.

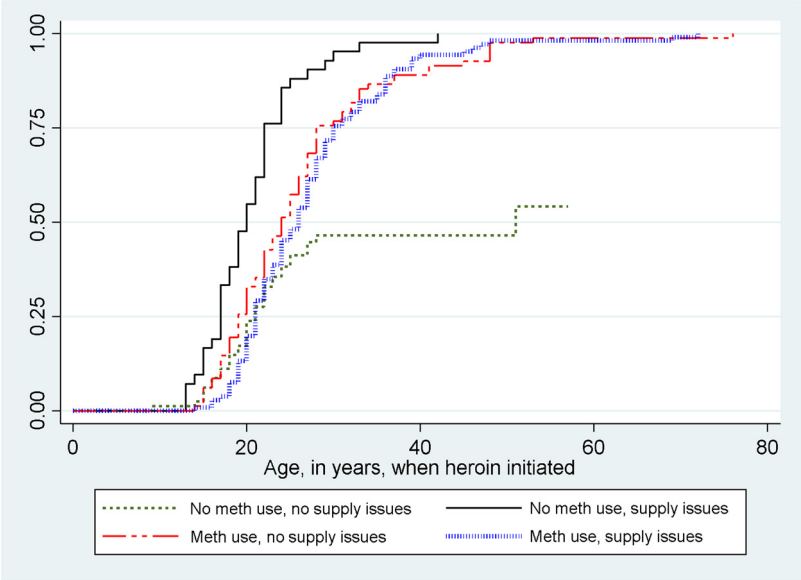

Fig. 2. Cumulative proportion of first heroin use among those with a history of pharmaceutical opioid use stratified by methamphetamine (meth) use and supply problems (%, Kaplan-Meier failure function).

methamphetamine in suburban relative to urban settings (Boeri and Gibson, 2009), our findings call for additional research on the process driving heroin initiation in the context of methamphetamine use and the recent increase in deaths associated with psychostimulant use (Kariisa et al., 2019).

Another factor associated with the delay in heroin initiation was having a history of SUD treatment prior to heroin use. This finding may reflect that through treatment, some individuals recognize a problematic history with alcohol and/or drugs and this recognition slows their progression to heroin initiation (Woodcock et al., 2015). It could also suggest that these individuals have health insurance coverage and hence better access to healthcare resources to reduce problematic substance use patterns, including receipt of SUD treatment (Gerstein and Lewin, 1990). While we do not know the extent to which individuals in our sample met the diagnostic criteria for opioid use disorder, these findings nonetheless suggest that expansion of medication-assisted treatment and other evidence-based substance use disorder treatment modalities could confer a protective effect.

One new finding was the accelerated time to heroin initiation among those whose rationale for heroin initiation included wanting to try a new method, try something new, or needing a break from the other method. Although not directly assessed in this study, some of these responses likely reflect changes to illicit drug markets since others have discussed increased heroin use in places with a limited supply of pharmaceutical opioids (Mars et al., 2014; Victor et al., 2017).

4.1. Limitations

There are some limitations to be considered. First, the retrospective design and the self-reporting of substance use limits our ability to make causal inferences. Our study was subject to recall bias, since the accuracy of the reported month and year of initiating heroin use and reasons for transitioning to heroin subsequent to pharmaceutical opioid use may have been limited for participants. However, such events are usually experienced as major life transitions (Fitzgerald et al., 1999), reducing the likelihood that participants had difficulty recalling them. Second, we did not consider the route of pharmaceutical opioid administration as a predictor of heroin initiation despite it being a significant factor in other studies (Monico and Mitchell, 2018; Surratt et al., 2017); although we found that other pharmaceutical opioid use characteristics were independently associated with heroin initiation including acquisition and age of first use. Third, our sampling approach including street-based recruitment and snowball/chain referral, as well as our conceptualization of suburban/exurban communities, limits the generalizability of our results. Half the sample experienced recent homelessness and nearly one-third reported non-opioid illicit drug use prior to their first opioid use, indicating a high-risk substance using population. Selection bias may have contributed to decreased generalizability but this bias appears minimal since the demographic composition of our sample (primarily non-Hispanic white males under 40 years of age) closely reflects the demographic profile of opioid-related overdose deaths and emergency department visits in California (California Department of Public Health, 2019). Most importantly, this study was intended to examine transitions from pharmaceutical opioid use to heroin, therefore by design our sample only included heroin users who had used pharmaceutical opioids prior to heroin initiation. Therefore, this study was unable to examine patterns related to heroin initiation in the absence of prior pharmaceutical opioid use.

4.2. Conclusions

This study showed that heroin initiation among individuals whose initial use of any opioid was a pharmaceutical opioid was dependent on several structural and behavioral factors. Most importantly, our results provide some support for the hypothesis that policies intended to improve prescribing behaviors, such as prescription drug monitoring programs and changes to opioid prescribing guidelines, may also affect the illicit supply of pharmaceutical opioids. The resulting restriction in the availability of pharmaceutical opioids may have unintentionally contributed to the initiation of illicit opioid use for some (Branham, 2018). The U.S. Food and Drug Administration has shared similar concerns with the warning that rapid discontinuation of prescribed pharmaceutical opioids can lead some patients to seek illicit opioids, such as heroin, to treat pain or withdrawal symptoms (U.S. Food and Drug Administration, 2019). Our work suggests that policies that may result in the loss of access to illicitly obtained pharmaceutical opioids without ensuring immediate access to evidence-based medication-assisted treatment, such as buprenorphine or methadone, could steer those with a long history of using NPPO towards heroin use. Overall, our study highlights the need for more targeted interventions to treat NPPO use and prevent heroin initiation, particularly for geographically dispersed communities lacking such services.

Contributors

PD and TG conceptualized study concept and design. TG conducted data analysis. TG and PD drafted the manuscript. All authors commented and contributed to critical revision of manuscript for important intellectual content.

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Declarations of Competing Interest

None.

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